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(54) Title: 5-BENZYL-OCTAHYDROINDOLE AND 6-BENZYL-DECAHYDROQUINOLINE NMDA/NR2B ANTAGONISTS

(57) Abstract: Novel 5-benzyl-octahydroindoles and 6-benzyl-decahydroquinolines substituted in the 1-position are effective as NMDA NR2B antagonists useful for relieving pain.

TITLE OF THE INVENTION

5-BENZYL-OCTAHYDROINDOLE AND 6-BENZYL-DECAHYDROQUINOLINE NMDA/NR2B ANTAGONISTS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to novel 5-benzyl-octahydroindoles and 6-benzyl-decahydroquinolines. In particular, this invention relates to novel 5-benzyl-octahydroindoles and 6-benzyl-decahydroquinolines substituted in the 1-position that are effective as NMDA NR2B antagonists useful for relieving pain.

Ions such as glutamate play a key role in processes related to chronic pain and pain-associated neurotoxicity – primarily by acting through N-methyl-D-aspartate ("NMDA") receptors. Thus, inhibition of such action – by employing ion channel antagonists, particularly NMDA antagonists – can be beneficial in the treatment and control of pain.

Known NMDA antagonists include ketamine, dextromophan, and 3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid ("CPP"). Although these compounds have been reported (J.D.Kristensen, et al., *Pain*, 51:249-253 (1992); K.Eide, et al., *Pain*, 61:221-228 (1995); D.J.Knox, et al., *Anaesth. Intensive Care* 23:620-622 (1995); and M.B.Max, et al., *Clin. Neuropharmacol.* 18:360-368 (1995)) to produce symptomatic relief in a number of neuropathies including postherpetic neuralgia, central pain from spinal cord injury, and phantom limb pain, widespread use of these compounds is precluded by their undesirable side effects. Such side effects at analgesic doses include psychotomimetic effects such as dizziness, headache, hallucinations, dysphoria, and disturbances of cognitive and motor function. Additionally, more severe hallucinations, sedation, and ataxia are produced at doses only marginally higher than analgesic doses. Thus, it would be desirable to provide novel NMDA antagonists that are absent of undesirable side effects or that produces fewer and/or milder side effects.

NMDA receptors are heteromeric assemblies of subunits, of which two major subunit families designated NR1 and NR2 have been cloned. Without being

bound by theory, it is generally believed that the various functional NMDA receptors in the mammalian central nervous system ("CNS") are only formed by combinations of NR1 and NR2 subunits, which respectively express glycine and glutamate recognition sites. The NR2 subunit family is in turn divided into four individual subunit types: NR2A, NR2B, NR2C, and NR2D. I. Ishii, et al., *J. Biol. Chem.*, 268:2836-2843 (1993), A.Wenel, et al., *Neural Report*, 7:45-48 (1995), and D.J.Laurie et al., *Mol. Brain Res.*, 51:23-32 (1997) describe how the various resulting combinations produce a variety of NMDA receptors differing in physiological and pharmacological properties such as ion gating properties, magnesium sensitivity, pharmacological profile, as well as in anatomical distribution.

For example, while NR1 is found throughout the brain, NR2 subunits are differentially distributed. In particular, it is believed that the distribution map for NR2B lowers the probability of side effects while producing pain relief. For example, S.Boyce, et al., *Neuropharmacology*, 38:611-623(1999) describes the effect of selective NMDA NR2B antagonists on pain with reduced side-effects. Thus, it would be desirable to provide novel NMDA antagonists that target the NR2B receptor.

International Patent Publication WO94/21615 describes benzimidazole-piperidine compounds utilized as dopamine D4 antagonists. Phenol compounds described as NMDA antagonists are described in U.S. patent Nos. 5,306,723 and 5,436,255, and in International Patent Publications WO91/17156, WO92/19502, WO93/02052, WO94/29571, WO95/28057, WO96/37226, and EP 04422506. Benzyl piperidines substituted with phenols or imidazoles are described in Z.-L. Zhou, et al., *J. Medicinal Chemistry*, 42:2993-3000(1999); T.F. Gregory, et al., Poster #94, 218th National Meeting American Chemical Society, New Orleans, Louisiana, August 22-26, 1999. Other NMDA NR2B selective compounds are described in European Patent Publication EP 787493 and *British J. Pharmacol.*, 123:463(1998). However, there continues to be a need for novel NMDA antagonists that target the NR2B receptor.

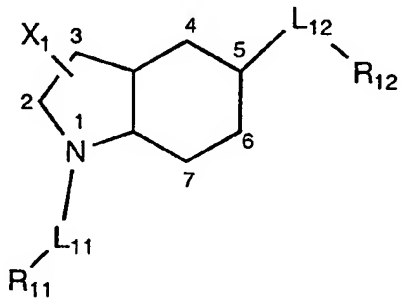
SUMMARY OF THE INVENTION

The present invention relates to 5-benzyl-octahydroindoles and 6-benzyl-decahydroquinolines substituted in the 1-position with benzimidazoles, imidazopyridines, phenols or imidazoles either directly or through a C_1-C_4alkyl, cycloalkyl, hydroxyalkyl, alkoxy or aminoalkyl chain. The present invention also

forms novel pharmaceutical compositions utilizing these novel compounds. Further, this invention includes novel methods to treat pain by utilizing the novel compounds.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the compounds of this invention are represented by Formula (I):



(I)

or pharmaceutically acceptable salts thereof, wherein

R_{11} is 2-benzimidazole, 4-imidazole, 2-imidazopyridine, 2-indole, 2-quinazoline, or 4-phenol; each optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

R_{12} is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

L_{11} is C_1-C_4alkyl, C_1-C_4alkenyl, C_1-C_4alkynyl, C_1-C_4alkoxy, aminoC_1-C_4alkyl, hydroxyC_1-C_4alkyl, carbonyl, cycloC_3-C_6alkyl or aminocarbonyl;

L_{12} is phenylmethyl or phenylmethylaminocarbonyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, or methyl; and

optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X_1, wherein X_1 is hydroxy, amino C_1-C_4alkylamino, di(C_1-C_4)alkylamino, C_1-C_4alkyl, ester, carbamate, carbonate, or ether.

In an embodiment, the compound of the invention is represented by Formula (I), or pharmaceutically acceptable salts thereof, wherein

R_{11} is 2-benzimidazole, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C4alkyl, trifluoromethyl, hydroxy, or carboxy;

R_{12} is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C4alkyl, trifluoromethyl, hydroxy, or carboxy;

L_{11} is C_1-C4alkyl, C_1-C4alkenyl, C_1-C4alkynyl, C_1-C4alkoxy, aminoC_1-C4alkyl, hydroxyC_1-C4alkyl, carbonyl, cycloC_3-C_6alkyl or aminocarbonyl;

L_{12} is phenylmethyl or phenylmethylaminocarbonyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, or methyl; and

optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X_1, wherein X_1 is hydroxy, amino C_1-C4alkylamino, di(C_1-C4)alkylamino, C_1-C4alkyl, ester, carbamate, carbonate, or ether.

In another embodiment, the compound of the invention is represented by Formula (I), or pharmaceutically acceptable salts thereof, wherein

R_{11} is 4-imidazole, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C4alkyl, trifluoromethyl, hydroxy, or carboxy;

R_{12} is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C4alkyl, trifluoromethyl, hydroxy, or carboxy;

L_{11} is C_1-C4alkyl, C_1-C4alkenyl, C_1-C4alkynyl, C_1-C4alkoxy, aminoC_1-C4alkyl, hydroxyC_1-C4alkyl, carbonyl, cycloC_3-C_6alkyl or aminocarbonyl;

L_{12} is phenylmethyl or phenylmethylaminocarbonyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, or methyl; and

optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X_1, wherein X_1 is hydroxy, amino C_1-C4alkylamino, di(C_1-C4)alkylamino, C_1-C4alkyl, ester, carbamate, carbonate, or ether.

In still another embodiment, the compound of the invention is represented by Formula (I), or pharmaceutically acceptable salts thereof, wherein

R_{11} is 4-phenol; optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

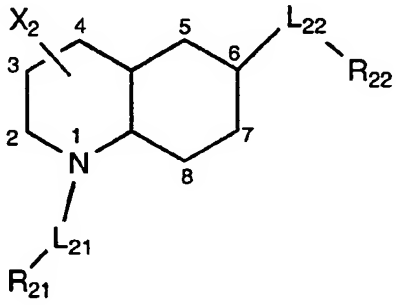
R_{12} is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

L_{11} is C_1-C_4alkyl, C_1-C_4alkenyl, C_1-C_4alkynyl, C_1-C_4alkoxy, aminoC_1-C_4alkyl, hydroxyC_1-C_4alkyl, carbonyl, cycloC_3-C_6alkyl or aminocarbonyl;

L_{12} is phenylmethyl or phenylmethylaminocarbonyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, or methyl; and

optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X_1, wherein X_1 is hydroxy, amino C_1-C_4alkylamino, di(C_1-C_4)alkylamino, C_1-C_4alkyl, ester, carbamate, carbonate, or ether.

In another aspect, the compounds of this invention are represented by Formula (II):



(II)

or pharmaceutically acceptable salts thereof, wherein

R_{21} is 2-benzimidazole, 4-imidazole, 2-imidazopyridine, 2-indole, 2-quinazoline, or 4-phenol; each optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

R_{22} is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

L_{21} is C_1-C_4alkyl, C_1-C_4alkenyl, C_1-C_4alkynyl, C_1-C_4alkoxy, aminoC_1-C_4alkyl, hydroxyC_1-C_4alkyl, carbonyl, cycloC_3-C_6alkyl or aminocarbonyl;

L_{22} is phenylmethyl or phenylmethylaminocarbonyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, or methyl; and

optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X2, wherein X_2 is hydroxy, amino, C_1-C_4alkylamino, di(C_1-C_4)alkylamino, C_1-C_4alkyl, ester, carbamate, carbonate, or ether.

In an embodiment, the compound of this invention is represented by Formula (II) or a pharmaceutically acceptable salt thereof, wherein

R_{21} is 2-benzimidazole, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

R_{22} is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

L_{21} is C_1-C_4alkyl, C_1-C_4alkenyl, C_1-C_4alkynyl, C_1-C_4alkoxy, aminoC_1-C_4alkyl, hydroxyC_1-C_4alkyl, carbonyl, cycloC_3-C_6alkyl or aminocarbonyl;

L_{22} is phenylmethyl or phenylmethylaminocarbonyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, or methyl; and

optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X2, wherein X_2 is hydroxy, amino C_1-C_4alkylamino, di(C_1-C_4)alkylamino, C_1-C_4alkyl, ester, carbamate, carbonate, or ether.

As used herein, "alkyl" as well as other groups having the prefix "alk" such as, for example, alkoxy, alkanoyl, alkenyl, alkynyl and the like, means carbon chains which may be linear or branched or combinations thereof. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, sec- and tert-butyl, pentyl, hexyl, heptyl and the like. "Alkenyl", "alkynyl" and other like terms include carbon chains containing at least one unsaturated C-C bond.

The term "cycloalkyl" means carbocycles containing no heteroatoms, and includes mono-, bi- and tricyclic saturated carbocycles, as well as fused ring systems. Such fused ring systems can include one ring that is partially or fully

unsaturated such as a benzene ring to form fused ring systems such as benzofused carbocycles. Cycloalkyl includes such fused ring systems as spirofused ring systems. Examples of cycloalkyl include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, decahydronaphthalene, adamantane, indanyl, indenyl, fluorenyl, 1,2,3,4-tetrahydronaphalene and the like. Similarly, "cycloalkenyl" means carbocycles containing no heteroatoms and at least one non-aromatic C-C double bond, and include mono-, bi- and tricyclic partially saturated carbocycles, as well as benzofused cycloalkenes. Examples of cycloalkenyl include cyclohexenyl, indenyl, and the like.

Unless otherwise stated, the terms "carbonyl" and "aminocarbonyl" include short C_1-C_2 termini. The terms include, for example, -CH_2CONH-, -CH_2CO-, -$C_2H_4CONHCH_2$-, and -$CH_2COC_2H_4$-.

Unless otherwise stated, the term "carbamate" is used to include -$OCOOC_1$-C_4alkyl, -$NHCOOC_1$-C_4alkyl, and -$OCONHC_1$-C_4alkyl.

The term "halogen" includes fluorine, chlorine, bromine and iodine atoms.

The term "SEM" is used to describe –CH_2–O–CH_2CH_2–$Si(CH_3)_3$.

The term "C_0" means that the carbon is not present. Thus, "C_0-C_5" means that there are from none to five carbons present – that is, five, four, three, two, one, or no carbons present.

The term "optionally substituted" is intended to include both substituted and unsubstituted. Thus, for example, optionally substituted aryl could represent a pentafluorophenyl or a phenyl ring.

Compounds described herein contain one or more asymmetric centers and may thus give rise to diastereomers and optical isomers. The present invention includes all such possible diastereomers as well as their racemic mixtures, their substantially pure resolved enantiomers, all possible geometric isomers, and pharmaceutically acceptable salts thereof. The above Formula I and Formula II are shown without a definitive stereochemistry at certain positions. The present invention includes all stereoisomers of Formula I and Formula II or pharmaceutically acceptable salts thereof. Further, mixtures of stereoisomers as well as isolated specific stereoisomers are also included. During the course of the synthetic procedures used to prepare such compounds, or in using racemization or epimerization procedures known to those skilled in the art, the products of such procedures can be a mixture of stereoisomers.

The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic bases or acids. When the compound of the present invention is acidic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic bases, including inorganic bases and organic bases. Salts derived from such inorganic bases include aluminum, ammonium, calcium, copper (ic and ous), ferric, ferrous, lithium, magnesium, manganese (ic and ous), potassium, sodium, zinc and the like salts. Particularly preferred are the ammonium, calcium, magnesium, potassium and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, as well as cyclic amines and substituted amines such as naturally occurring and synthesized substituted amines. Other pharmaceutically acceptable organic non-toxic bases from which salts can be formed include ion exchange resins such as, for example, arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like.

When the compound of the present invention is basic, its corresponding salt can be conveniently prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include, for example, acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid and the like. Particularly preferred are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, and tartaric acids.

The pharmaceutical compositions of the present invention comprise a compound represented by Formula I or Formula II (or pharmaceutically acceptable salts thereof) as an active ingredient, a pharmaceutically acceptable carrier and optionally other therapeutic ingredients or adjuvants. The compositions include compositions suitable for oral, rectal, topical, and parenteral (including subcutaneous, intramuscular, and intravenous) administration, although the most suitable route in any given case will depend on the particular host, and nature and severity of the conditions for which the active ingredient is being administered. The pharmaceutical

compositions may be conveniently presented in unit dosage form and prepared by any of the methods well known in the art of pharmacy.

In practice, the compounds represented by Formula I or Formula II, or pharmaceutically acceptable salts thereof, of this invention can be combined as the active ingredient in intimate admixture with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral or parenteral (including intravenous). Thus, the pharmaceutical compositions of the present invention can be presented as discrete units suitable for oral administration such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient. Further, the compositions can be presented as a powder, as granules, as a solution, as a suspension in an aqueous liquid, as a non-aqueous liquid, as an oil-in-water emulsion or as a water-in-oil liquid emulsion. In addition to the common dosage forms set out above, the compound represented by Formula I or Formula II, or pharmaceutically acceptable salts thereof, may also be administered by controlled release means and/or delivery devices. The compositions may be prepared by any of the methods of pharmacy. In general, such methods include a step of bringing into association the active ingredient with the carrier that constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both. The product can then be conveniently shaped into the desired presentation.

Thus, the pharmaceutical compositions of this invention may include a pharmaceutically acceptable carrier and a compound or a pharmaceutically acceptable salt of Formula I or Formula II. The compounds of Formula I or Formula II, or pharmaceutically acceptable salts thereof, can also be included in pharmaceutical compositions in combination with one or more other therapeutically active compounds.

The pharmaceutical carrier employed can be, for example, a solid, liquid, or gas. Examples of solid carriers include lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Examples of liquid carriers are sugar syrup, peanut oil, olive oil, and water. Examples of gaseous carriers include carbon dioxide and nitrogen.

In preparing the compositions for oral dosage form, any convenient pharmaceutical media may be employed. For example, water, glycols, oils, alcohols,

flavoring agents, preservatives, coloring agents and the like may be used to form oral liquid preparations such as suspensions, elixirs and solutions; while carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to form oral solid preparations such as powders, capsules and tablets. Because of their ease of administration, tablets and capsules are the preferred oral dosage units whereby solid pharmaceutical carriers are employed. Optionally, tablets may be coated by standard aqueous or nonaqueous techniques

A tablet containing the composition of this invention may be prepared by compression or molding, optionally with one or more accessory ingredients or adjuvants. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. Each tablet preferably contains from about 1mg to about 500mg of the active ingredient and each cachet or capsule preferably containing from about 1 to about 500mg of the active ingredient.

Pharmaceutical compositions of the present invention suitable for parenteral administration may be prepared as solutions or suspensions of the active compounds in water. A suitable surfactant can be included such as, for example, hydroxypropylcellulose. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, and mixtures thereof in oils. Further, a preservative can be included to prevent the detrimental growth of microorganisms.

Pharmaceutical compositions of the present invention suitable for injectable use include sterile aqueous solutions or dispersions. Furthermore, the compositions can be in the form of sterile powders for the extemporaneous preparation of such sterile injectable solutions or dispersions. In all cases, the final injectable form must be sterile and must be effectively fluid for easy syringability. The pharmaceutical compositions must be stable under the conditions of manufacture and storage; thus, preferably should be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), vegetable oils, and suitable mixtures thereof.

Pharmaceutical compositions of the present invention can be in a form suitable for topical use such as, for example, an aerosol, cream, ointment, lotion, dusting powder, or the like. Further, the compositions can be in a form suitable for use in transdermal devices. These formulations may be prepared, utilizing a compound represented by Formula I or Formula II of this invention, or pharmaceutically acceptable salts thereof, via conventional processing methods. As an example, a cream or ointment is prepared by mixing hydrophilic material and water, together with about 5 wt% to about 10 wt% of the compound, to produce a cream or ointment having a desired consistency.

Pharmaceutical compositions of this invention can be in a form suitable for rectal administration wherein the carrier is a solid. It is preferable that the mixture forms unit dose suppositories. Suitable carriers include cocoa butter and other materials commonly used in the art. The suppositories may be conveniently formed by first admixing the composition with the softened or melted carrier(s) followed by chilling and shaping in moulds.

In addition to the aforementioned carrier ingredients, the pharmaceutical formulations described above may include, as appropriate, one or more additional carrier ingredients such as diluents, buffers, flavoring agents, binders, surface-active agents, thickeners, lubricants, preservatives (including anti-oxidants) and the like. Furthermore, other adjuvants can be included to render the formulation isotonic with the blood of the intended recipient. Compositions containing a compound described by Formula I or Formula II, or pharmaceutically acceptable salts thereof, may also be prepared in powder or liquid concentrate form.

Experimental Protocols

Assessing the Activity of Selected Compounds to Inhibit NR1A/2B NMDA Receptor Activation (FLIPR Assay)

The activity of selected compounds to inhibit NR1A/2B NMDA receptor activation measured as NR1A/2B receptor-mediated Ca^{2+} influx is assessed by the following procedure:

NR1A/2B receptor transfected L(tk) cells are plated in 96-well format at 3 x 10^6 cells per plate and grown for one - two days in normal growth media (Dulbeccos MEM with Na pyruvate, 4500 mgglucose, pen/strep, glutamine, 10% FCS

and 0.5mg/ml geneticin). NR1A/2B-expression in these cells is induced by the addition of 4nM dexamethasone in the presence of 500μM ketamine for 16 - 24 hours. After receptor induction cells are washed using a Labsystem Cellwasher two times with assay buffer (Hanks balanced salt solution (HBSS-Mg^{++} free) containing 20mM HEPES, 0.1% BSA, 2mM $CaCl_2$ and 250μM probenecid). The cells of each 96 well cell plate are loaded with the Ca^{++} sensitive dye Fluo-3 (Molecular Probes, Inc.) at 4μM in assay buffer containing 0.5% FBS, and 0.04% pluronic F-127 (Molecular Probes, Inc.) for 1h at 37 °C avoiding light. The cells are then washed with the Cellwasher four times with assay buffer leaving them in 100μl buffer. Test compounds in solution are pipetted by FLIPR (Fluorometric Imaging Plate Reader) into each test well for a 2min pretreatment. During this time the fluorescence intensity is recorded (excitation at 488nm and emission at 530nm). The glutamate/glycine 50μL agonist solution (final concentration 1μM/1μM) is then added by FLIPR into each well already containing 150μL of buffer (containing the test compound or vehicle) and the fluorescence is continuously monitored for 10min. The endpoint fluorescence values are used to determine an IC_{50} value comparing the agonist-stimulated signal for the vehicle alone sample and that for the cells incubated with each concentration of test compound.

Determining the Apparent Dissociation Constant (Ki) of Compounds for Human NR1A/NR2B Receptors (Binding Assay):

The radioligand binding assay is performed at room temperature in 96-well microtiter plates with a final assay volume of 1.0mL in 20mM Hepes buffer (pH 7.4) containing 150mM NaCl. Solutions of test compounds were prepared in DMSO and serially diluted with DMSO to yield 20μL of each of 10 solutions differing by 3-fold in concentration. Non-specific binding (NSB) using hot AMD-1 (10μM final concentration) and total binding (TB) by using DMSO (2% final concentration). A solution of NR1A/NR2B receptors (40pM final concentration) and tritiated AMD-2 (1nM final concentration) were added to the test compounds. After 3h of incubation at room temperature, samples are filtered through Packard GF/B filters (presoaked in 0.05% PEI, polyethyleninine Sigma P-3143) and washed 10 times with 1mL of cold 20mM Hepes buffer per wash. After vacuum drying of the filter plates, 40μL of Packard Microscint-20 was added and bound radioactivity determined in a Packard

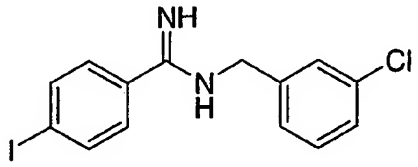
TopCount. The apparent dissociation constant (Ki), the maximum percentage inhibition ($\%I_{max}$), the minimum percentage inhibition ($\%I_{min}$) and the hill slope (nH) were determined by a non-linear least squares fitting the bound CPM data to Equation #1 below.

Equation#1:

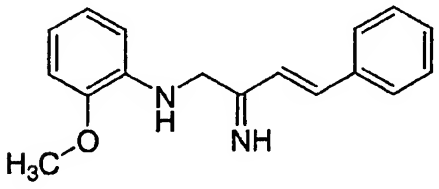
$$\text{CPM Bound} = \frac{(SB)\,(\%I_{max} - \%I_{min})}{(1 + ([\text{Drug}] / (Ki\ [\text{L-844,345}]/K_D))^{nH})} + NSB + (SB)\,(1 - \%I_{max})$$

where, K_D is the apparent dissociation constant for the radioligand for the receptor as determined by hot saturation and SB is the specifically bound CPM determined from the difference of TB and NSB.

AMD-1

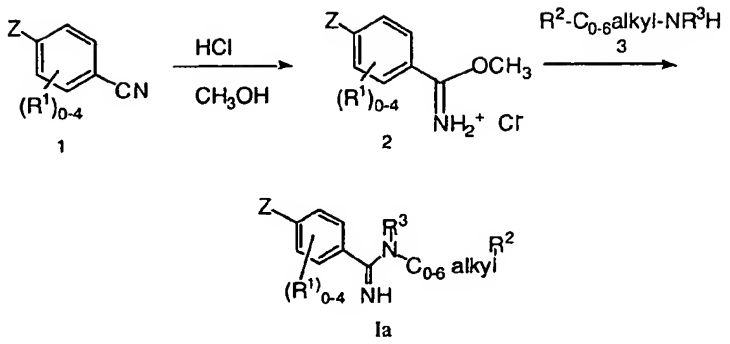


AMD-2



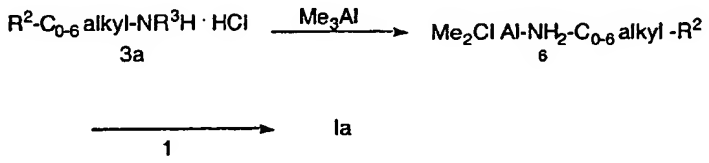
Compounds AMD-1 and AMD-2 can be synthesized in accordance with the following general reaction schemes.

SCHEME 1



In accordance with scheme 1, hydrogen chloride is bubbled through a solution of the appropriately substituted benzonitrile 1 in methanol at room temperature. The volatiles are removed under reduced pressure and the resulting residue is triturated with ether and filtered to yield the desired imidate 2. Imidate 2 is dissolved in methanol at ambient temperature, treated with amine 3 at ambient temperature and stirred under argon. The volatiles are removed under reduced pressure and the residue purified by preparative HPLC or trituration with ether to afford amidine Ia.

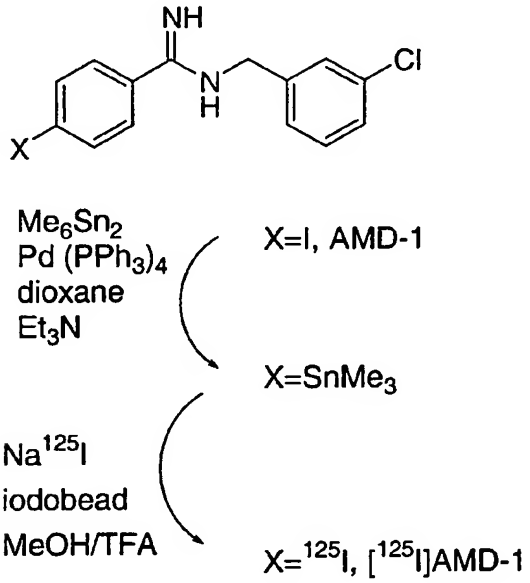
SCHEME 2



In accordance with scheme 2, at room temperature under argon, amine 3a is dissolved in ether and was treated with 1-M hydrogen chloride in ether (1 equiv.) in a single portion. The resulting precipitate is stirred vigorously for 10 minutes. The volatiles are removed under reduced pressure. The residue is suspended in toluene, cooled to 0°C under argon, treated with 2.0-M trimethylaluminum (1.05 equiv.) in a dropwise manner, and stirred for 45 minutes at room temperature to afford

intermediate 6 (not isolated). Compound 6 is added to a solution of nitrile 1 in toluene. The reaction is heated to 80°C without stirring in a sealed tube for 18h, cooled to ambient temperature, poured onto a silica gel column and eluted with methanol/dichloromethane to give the amidine 4.

Preparation of [^{125}I]AMD-1



Tritiated AMD-1 was prepared by the following procedure: A mixture of AMD-1, hydrochloride salt, (5mg, 0.012mmol) in dioxane (0.2mL) containing triethylamine (4μL) was treated with hexamethylditin (5μL), a catalytic amount of palladium catalyst and heated at 100°C for 45 minutes. The reaction was cooled to room temperature, filtered through a glass wool plug, rinsed with methanol and concentrated *in vacuo* to give 10.7mg of a brown oil. The oil was dissolved in methylene chloride and passed through a small silica column eluting with methylene chloride followed by 5% methanol/methylene chloride. Fractions containing the trimethylstannane (Rf 0.26 in 10% methanol/methylene chloride) were pooled and concentrated *in vacuo* to give 4.5mg of the trimethylstannane as a clear colorless oil. This material was further purified by HPLC (C18 Econosil, 10x250mm, 20 minute

linear gradient, 30% MeCN:70% H_2O (0.1% TFA) to 90% MeCN, 3mL/min, 254nm, retention time 15 minutes) to give 3mg of the trimethylstannane.

A $Na^{125}I$ shipping vial (10mCi, Amersham) was charged with a stir bar, an iodobead, 50μL of methanol and stirred five minutes at room temperature. A solution of the trimethylstannane (0.1mg) in 50μL of methanol containing 5μL of trifluoroacetic acid was added and the reaction was stirred for five minutes. The reaction was quenched with 50μL of ammonium hydroxide and purified by HPLC (C18 Vydac protein and peptide column, 4.6 x 250 mm, 20 minute linear gradient, 30% MeCN:70% H_2O (0.1% TFA) to 90% MeCN, 1mL/min, retention time 11minutes). Fractions containing the radioactive product were pooled and concentrated *in vacuo* to give 989μCi of [^{125}I]AMD-1 with a specific activity of 898Ci/mmol as measured by UV absorbance at 272nm.

Synthesis of Tritiated AMD-2

Tritiated AMD-2 was prepared by the following procedure: The phenol of AMD-2 (2mg, 0.008mmol) dissolved in dimethylformamide (0.6mL) and potasium carbonate (1.2mg) for 1hr. High specific activity tritiated methyl iodide (50mCi, 0.0006mmol, in toluene 1mL, American Radiolabeled Chemicals) was added at room temperature and stirred for 2 hours. The reaction mixture was filtered using a Whatman PTFE 0.45μm syringeless filter device to remove any insoluable potassium carbonate, washed with Abs. ethanol (2mL, Pharmco), and the combined filtrates were concentrated to dryness at room temperature using a rotary evaporator; this also removed any unreacted tritiated methyl iodide. The residue was purified by HPLC chromatography on a Phenomenx Luna C8 semi-prep column (Luna 5 micro C8(2), 250x10.0 mm) using a gradient system of 20/80 acetonitrile/water with 0.1% trifluoroacetic acid to 100% acetronitrile with 0.1% trifluoroacetic acid in 20min. Total activity of the product was 8mCi. Further purification was effected by absorption onto a Waters C-18 Sep-pak column (Waters Sep-Pak PLUS C18) and elution with water followed by absolute ethanol. The product was diluted with absolute ethanol (10mL) before submission for final analysis.

The compounds of this invention exhibit less than 50μM in the FLIBR and binding assays. Thus, the compounds and pharmaceutical compositions of this invention have been found to exhibit biological activity as NMDA NR2B antagonists.

Accordingly, another aspect of the invention is the treatment of pain, migraine, depression, anxiety, schizophrenia, Parkinson's disease, or stroke – maladies that are amenable to amelioration through inhibition of NMDA NR2B receptors – by the administration of an effective amount of the compounds of this invention.

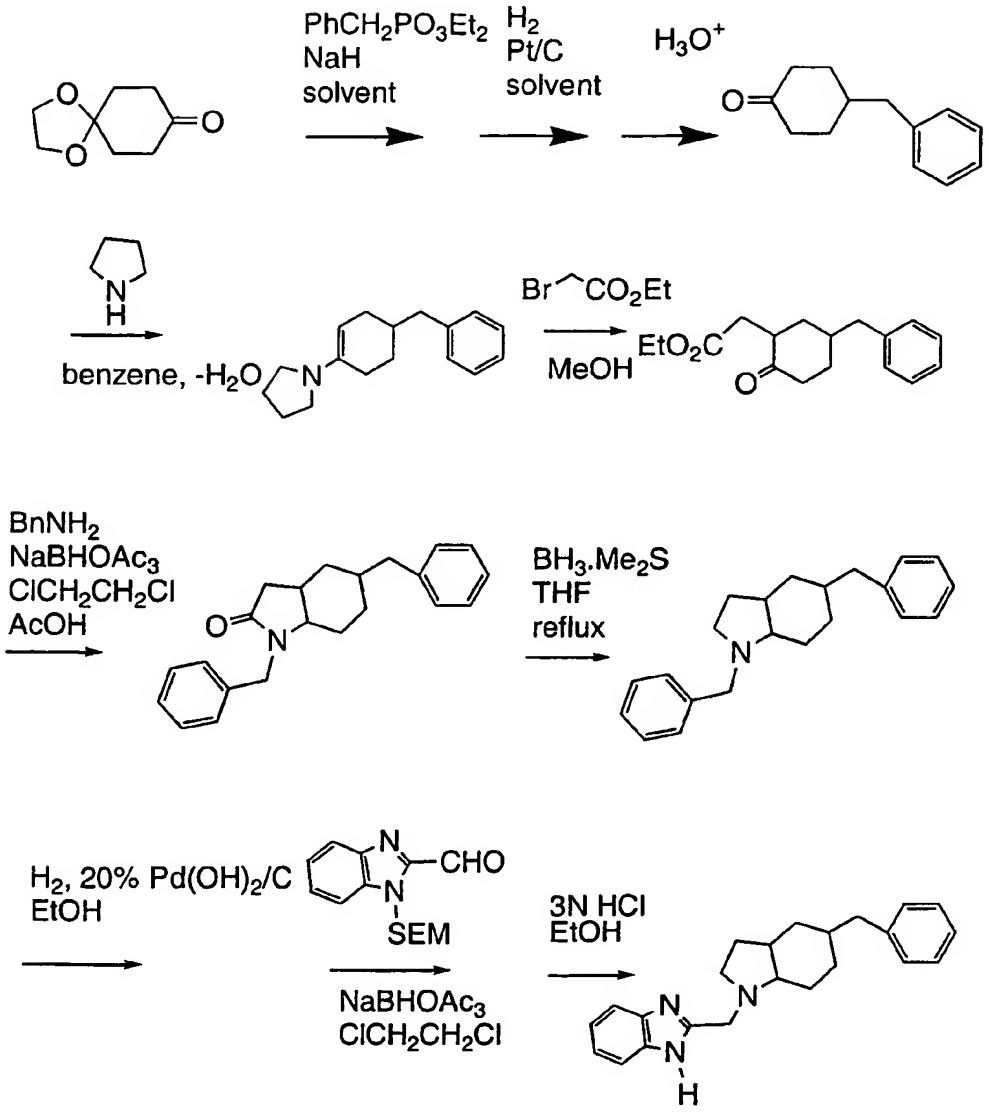
The following examples are provided to more fully illustrate the present invention, and are not to be construed as limiting the scope of the claims in any manner.

EXAMPLES

Preparation of 5-benzyl-octahydroindoles.

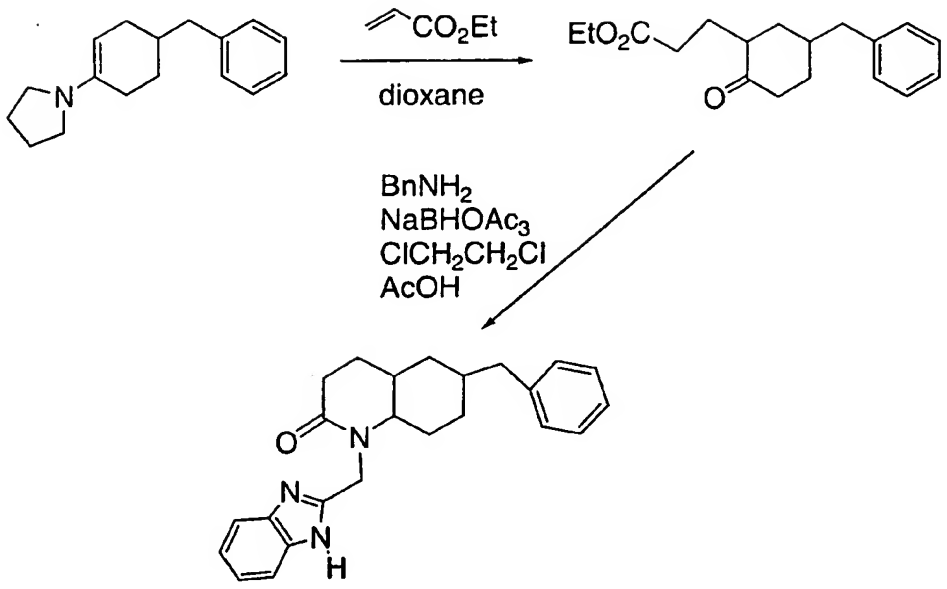
In one Example, 5-benzyl-octahydroindoles were prepared by Scheme 1 shown below:

Scheme 1

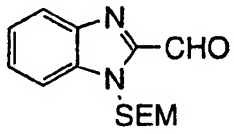


In another Example, 6-benzyl-decahydroquinolines were prepared by Scheme 2 shown below:

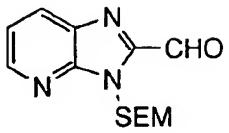
Scheme 2

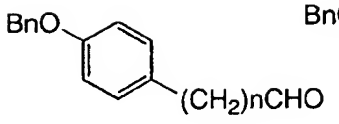


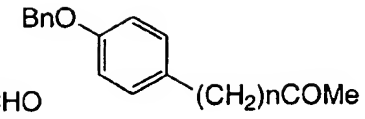
In Schemes 1 and 2 above, in place of the 1-SEM-benzimidole-2-carboxaldehyde



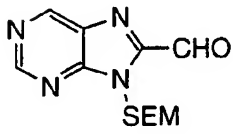
any of the following aldehydes, ketones, or bromides can be used to prepare the compounds of this invention:

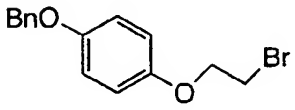


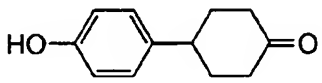


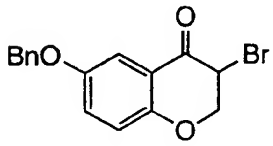


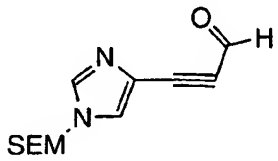
n = 0,1,2,3

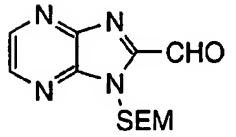


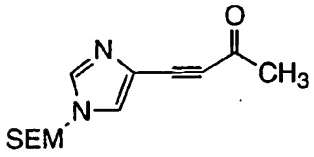


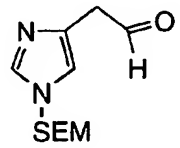


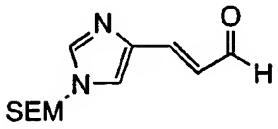


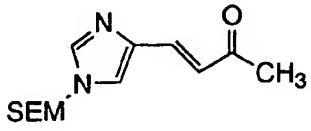


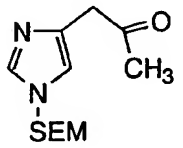


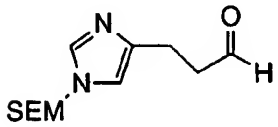


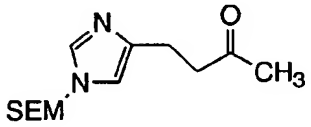




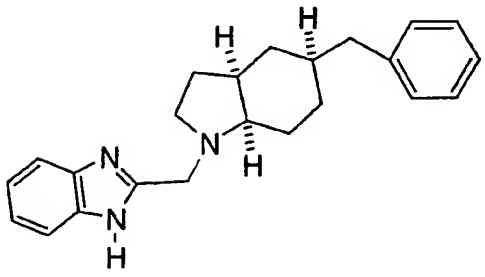




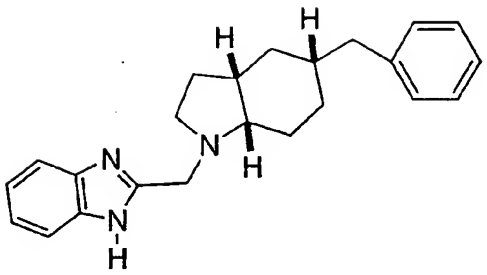




EXAMPLE 1



(Ex. 1A)

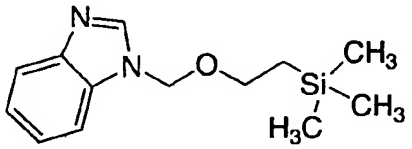


(Ex. 1B)

2-(5-cis-Benzyl-cis-octahydro-indol-1-ylmethyl)-1H-benzimidazole

Example 1 was prepared by the following procedure.

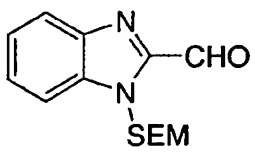
Step 1:



1-(2-Trimethylsilylethoxymethyl)-1H-benzimidazole:

A mixture of KH, from 7g of 30% oil dispersion, and 5g of benzimidazole in 100mL of THF was stirred under nitrogen at room temperature for 18h. To the stirred suspension was added 7g of 2-trimethylsilylethoxymethyl chloride and the mixture kept at room temperature for 24h, cooled in an ice bath, cautiously quenched with 50mL of water, and extracted into ether. The combined ether extracts were dried over $MgSO_4$ and concentrated. Low pressure chromatography over silica gel eluting with a gradient of 3:1 ethyl acetate:hexane to 100% ethyl acetate gave 9.5g of 1-SEM-benzimidazole as a colorless oil.

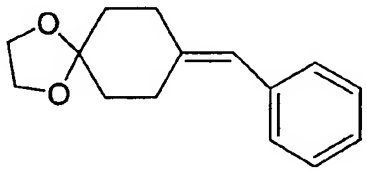
Step 2:



1-(2-Trimethylsilylethoxymethyl)-1H-benzimidazole-2-carbaldehyde:

To a solution of 40mmole of lithium diisopropylamide in 100mL of THF cooled to -78°C was added 5g of 1-SEM-benzimidazole in 50mL of THF. After 1.5h at or below -70°C, the red solution was quenched by rapid addition of 6mL of methyl formate. After warming to room temperature over 30min, 50mL of water and 200mL of ethyl acetate were added. The organic layer was separated and dried over $MgSO_4$, then concentrated under reduced pressure to 5.3g of a thick oil that solidified in the freezer.

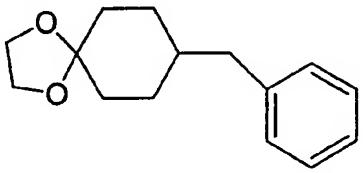
Step 3:



8-Benzylidene-1,4-dioxa-spiro[4.5]decane:

To a stirred solution of 20g of 1,4-dioxa-spiro[4.5]decan-8-one and 35g of diethyl benzylphosphonate in 60mL of 1,3-dimethyl-2-imidazolidinone dried over 4Å mol sieves was added 7g of 60% NaH oil dispersion. The mixture was allowed to stir overnight, diluted with 500mL of water and extracted with 3X100mL of ether. Combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Chromatography over silica gel eluting with a gradient of 5:95 ethyl acetate:hexane to 1:3 ethyl acetate:hexane gave 28g of olefin as a colorless oil.

Step 4:

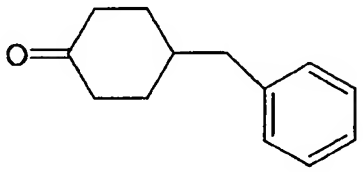


8-Benzyl-1,4-dioxa-spiro[4.5]decane:

A solution of 28g of 8-benzylidene-1,4-dioxa-spiro[4.5]decane and 1g of 5% palladium on carbon in 250mL of ethanol was allowed to stir overnight under

1atm of hydrogen. The catalyst was filtered off and the solution concentrated to give 28g of 8-benzyl-1,4-dioxa-spiro[4.5]decane as an oil.

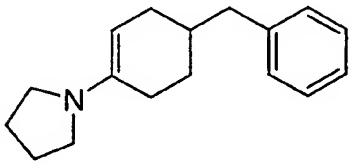
Step 5:



4-Benzyl-cyclohexanone:

A mixture of 28g of 8-benzyl-1,4-dioxa-spiro[4.5]decane, 100mL of water, 10mL of methanol and 20g of Amberlite® IR-120$^+$ was heated to reflux for 5h. After cooling, removal of solvents under reduced pressure gave 24g of 4-benzyl-cyclohexanone as an oil.

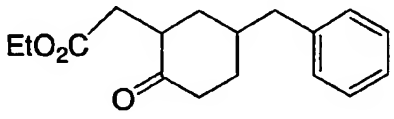
Step 6:



1-(4-Benzyl-cyclohex-1-enyl)-pyrrolidine:

A mixture of 5g of 4-benzyl-cyclohexanone, 3.5g of pyrrolidine, 500mL of benzene and 10mg of p-toluenesulfonic acid monohydrate was heated under a water separator apparatus for 48h, removing the distillate periodically until there was about 50mL remaining. The solution was cooled and concentrated to 8g of an amber liquid. The NMR was consistent with complete conversion to the enamine.

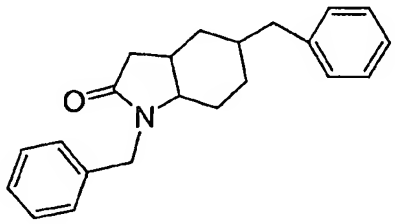
Step 7:



(5-Benzyl-2-oxo-cyclohexyl)-acetic acid ethyl ester:

A solution of 8g of the crude 1-(4-benzyl-cyclohex-1-enyl)-pyrrolidine and 7g of ethyl bromoacetate in 20mL of dioxane was heated at reflux for 12h, cooled and concentrated under reduced pressure. The residue was diluted with 10mL of water and 10mL of 10% sulfuric acid and extracted into 2X100mL of ether. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Evaporative distillation at oven temperature 150-170°C at 1mm gave 8g of (5-benzyl-2-oxo-cyclohexyl)-acetic acid ethyl ester as a thick oil.

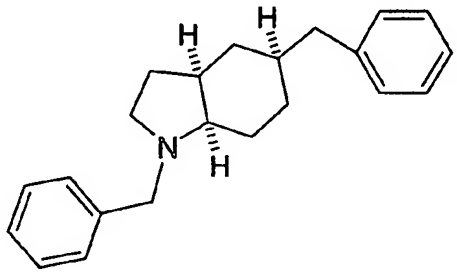
Step 7:

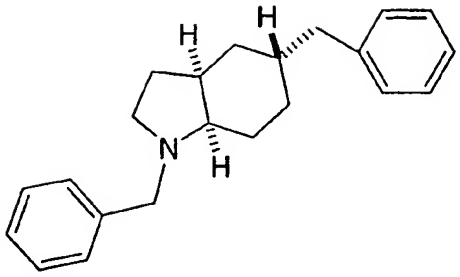


1,5-Dibenzyl-octahydro-indol-2-one:

A mixture of 8g of (5-benzyl-2-oxo-cyclohexyl)-acetic acid ethyl ester, 3.4g of acetic acid, 3.75g of benzylamine, 50mL of 1,2-dichloroethane and 7.7g of sodium triacetoxyborohydride was stirred at room temperature for 48h. The reaction mixture was diluted with 100mL chloroform and 40mL saturated aqueous Na_2CO_3 and the layers separated. The aqueous layer was extracted with 2X25mL of chloroform and the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure. Purification by chromatography eluting with 50% ethyl acetate in hexane gave 5g of 1,5-dibenzyl-octahydro-indol-2-one.

Step 7:

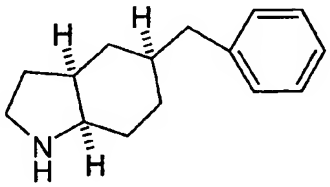




(±)-1,5-Dibenzyl-cis-octahydro-indole:

To a stirred solution of 5g of 1,5-dibenzyl-octahydro-indol-2-one in 50mL of dry THF was added 2.5mL of borane methyl sulfide. After stirring overnight, the mixture was heated to reflux for 1h, cooled in an ice bath, and cautiously quenched with 50mL of 6N HCl. After stirring and warming to room temperature for 2h, the mixture was warmed to reflux for 2h, cooled in an ice bath and the pH adjusted to 10 by addition of 10 N NaOH. The resulting mixture was extracted with 2X500mL of chloroform and the extracts dried over magnesium sulfate and concentrated under reduced pressure. Chromatography using a gradient of 50% ethyl acetate in hexane, 100% ethyl acetate then 10% methanol in ethyl acetate gave first 3.25g of (±)-cis-1,5-dibenzyl-cis-octahydro-indole as an oil, then in later fractions 1.15g of (±)-trans-1,5-dibenzyl-cis-octahydro-indole as an oil

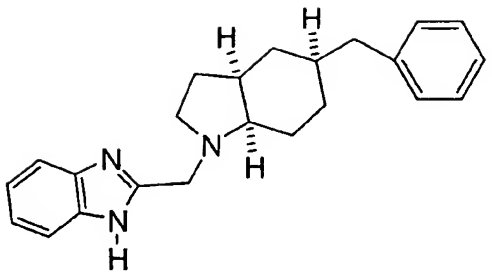
Step 8:

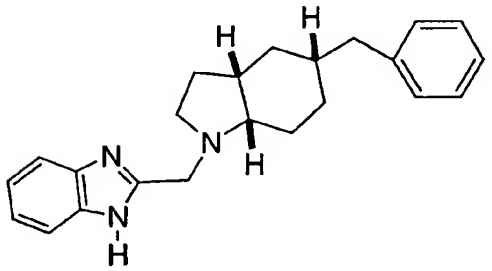


(±)-cis-5-Benzyl-cis-octahydro-indole:

A mixture of 0.65g of (±)-cis-1,5-dibenzyl-cis-octahydro-indole and 0.5g of 20% palladium hydroxide on carbon was shaken under 55psi of hydrogen for 18h. Filtration and concentration under reduced pressure gave 0.5g of (±)-cis-5-benzyl-cis-octahydro-indole as an oil.

Step 9:





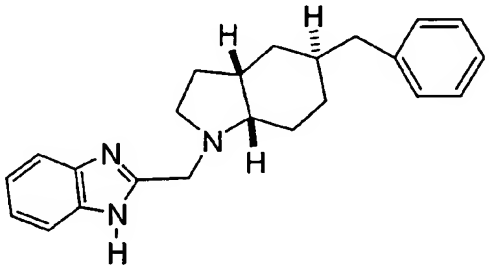
2-(5-cis-Benzyl-cis-octahydro-indol-1-ylmethyl)-1H-benzimidazole:

A mixture of 0.2g of (±)-cis-5-benzyl-cis-octahydro-indole, 0.3g of 1-(2-trimethylsilylethoxymethyl)-1H-benzimidazole-2-carbaldehyde, 5mL of 1,2-dichloroethane and 0.35g of sodium triacetoxyborohydride was stirred at room temperature for 48h. The reaction mixture was diluted with 50mL chloroform and 10mL saturated aqueous Na_2CO_3 and the layers separated. The aqueous layer was extracted with 2X25mL of chloroform and the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure. The crude SEM ether was heated to reflux in 50mL of ethanol containing 5mL of 3N HCl for 2h, cooled, concentrated and partitioned between 10mL of saturated aqueous Na_2CO_3 and 3X25mL of chloroform. The chloroform extracts were dried over magnesium sulfate and concentrated. Purification by chromatography eluting with 90:10 $CHCl_3$:MeOH gave 0.35g of (±)-2-(5-cis-benzyl-cis-octahydro-indol-1-ylmethyl)-1H-benzimidazole as a solid after trituration with ether-hexane.

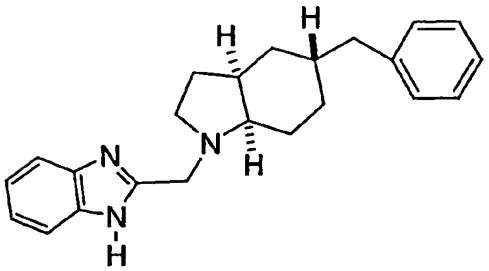
Chromatography on a Chiralpak™ AD column eluting with a 70:30 mixture of 0.1% TFA in hexane and ethanol followed by conversion to the free base gave 0.15g of 2-(5-cis-benzyl-cis-octahydro-indol-1-ylmethyl)-1H-benzimidazole, enantiomer A:RT = 4.22min; MS (m+1) = 346.3; ^1H NMR (400MHz, $CDCl_3$) 9.4 (br, 1H), 7.75 (br, 1H), 7.5 (br, 1H), 7.25 (m, 7H), 4.2 (d, 1H), 3.6 (d, 1H), 3.2 (br, 1H), 2.5 (m, 2H), 2.35 (br s, 1H), 2.1-1.2 (complex, 11H).

Later fractions gave 2-(5-cis-benzyl-cis-octahydro-indol-1-ylmethyl)-1H-benzimidazole, enantiomer B: RT = 7.22min; MS (m+1) = 346.3; ^{1}H NMR (400MHz, $CDCl_3$) 9.4 (br, 1H), 7.75 (br, 1H), 7.5 (br, 1H), 7.25 (m, 7H), 4.2 (d, 1H), 3.6 (d, 1H), 3.2 (br, 1H), 2.5 (m, 2H), 2.35 (br s, 1H), 2.1-1.2 (complex, 11H).

EXAMPLE 2



(Ex. 2A)

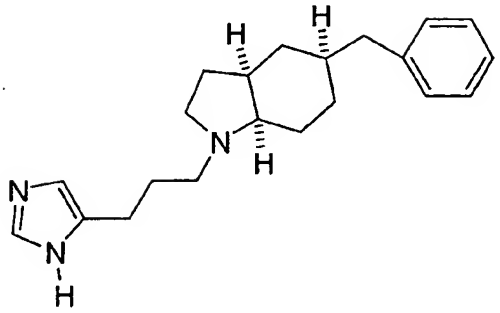


(Ex. 2B)

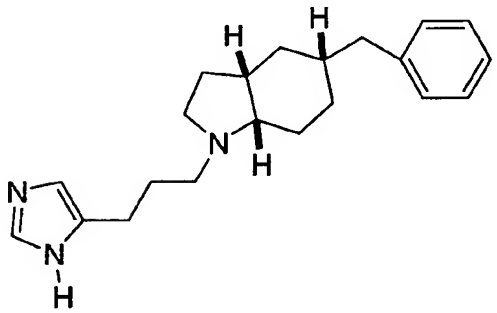
2-(5-trans-Benzyl-cis-octahydro-indol-1-ylmethyl)-1H-benzimidazole

Example 2 was prepared from (±)-trans-1,5-dibenzyl-cis-octahydro-indole following the procedures described for Example 1, Steps 8 and 9. This gave (±)-2-(5-trans-benzyl-cis-octahydro-indol-1-ylmethyl)-1H-benzimidazole: RT = 7.15 and 9.23min on Chiralpak™ AD (70:30 0.1% TFA in hexane: 2-propanol); MS (m+1) = 346.3; ^{1}H NMR (400MHz, $CDCl_3$) 10 (br, 1H), 7.6 (br, 2H), 7.25 (m, 7H), 4.05 (s, 2H), 3.6 (m, 1H), 2.95 (m, 2H), 2.85 (m, 1H), 2.0-0.9 (complex, 11H).

EXAMPLE 3



(Ex. 3A)



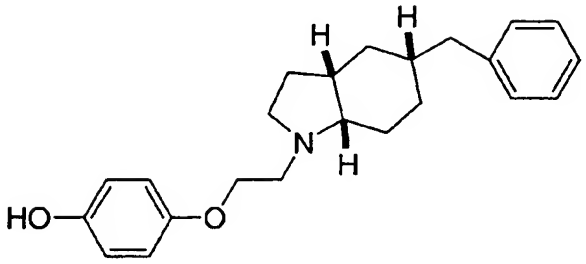
(Ex. 3B)

(±)-5-cis-Benzyl-1-[3-(3H-imidazol-4-yl)-propyl]-cis-octahydro-indole

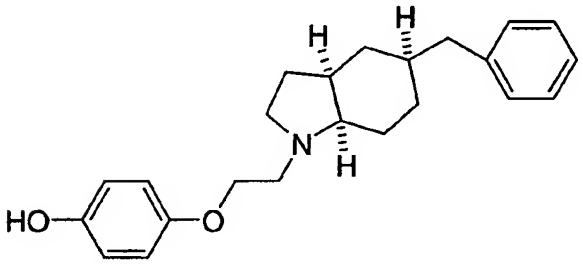
Example 3 was prepared by the following procedure. A mixture of 0.30g of (±)-cis-5-benzyl-cis-octahydro-indole, 0.8g of 3-(1H-imidazol-4-yl)-propionaldehyde, 5mL of 1,2-dichloroethane and 0.5g of sodium triacetoxyborohydride was stirred at room temperature for 48h. The reaction mixture was diluted with 50mL chloroform and 10mL saturated aqueous Na_2CO_3 and the layers separated. The aqueous layer was extracted with 2X25mL of chloroform and the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure. Purification by chromatography eluting with 90:10:1 $CHCl_3$:MeOH:NH_4OH gave 0.25g of (±)-5-benzyl-1-[3-(3H-imidazol-4-yl)-propyl]-octahydro-indole as a resin. MS (m+1) = 324.4; ^1H NMR (400MHz, $CDCl_3$) 7.42 (s,

1H), 7.2 (m, 5H), 6.75 (s, 1H), 3.22 (dd, 1H), 3.05 (m, 1H), 2.9 (m, 1H), 2.8-1.2 (complex, 17 H).

EXAMPLE 4



(Ex.4A)



(Ex. 4B)

4-[2-(5-Benzyl-octahydro-indol-1-yl)-ethoxy]-phenol

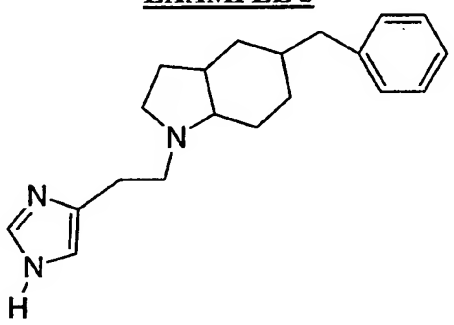
A mixture of 0.7g of (±)-cis-5-benzyl-cis-octahydro-indole, 0.3g of 1-(2-bromo-ethoxy)-4-benzyloxybenzene, 10mL of acetonitrile and 0.3g of potassium carbonate was stirred at reflux for 24h. The reaction mixture was cooled, concentrated, diluted with 50mL chloroform and 10mL saturated aqueous Na_2CO_3 and the layers separated. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure. Hydrogenation at 1atm over 0.2g of 10% Pd/C in 50mL of ethanol gave 0.12g of (±)-4-[2-(5-cis-benzyl-cis-octahydro-indol-1-yl)-ethoxy]-phenol after purification by chromatography eluting with 90:10

$CHCl_3$:MeOH: MS (m+1) = 352.3; ^1H NMR (400MHz, $CDCl_3$) 7.3 (s, 5H), 7.2 (dd, 2H), 6.8 (dd, 2H), 4.0 (br t, 2H), 3.3, (br, 1H), 3.1 (br, 1H), 2.5-1.2 (13H).

Chromatography on a Chiralpak™ OJ column eluting with a gradient of 70:30 to 30:70 hexane and 2-propanol gave 4-[2-(5-cis-benzyl-cis-octahydro-indol-1-yl)-ethoxy]-phenol, enantiomer A: RT = 11.3min; MS (m+1) = 352.3; ^1H NMR (400MHz, $CDCl_3$) 7.3 (s, 5H), 7.2 (dd, 2H), 6.8 (dd, 2H), 4.0 (br t, 2H), 3.3, (br, 1H), 3.1 (br, 1H), 2.5-1.2 (13H).

Later fractions gave 4-[2-(5-cis-benzyl-cis-octahydro-indol-1-yl)-ethoxy]-phenol, enantiomer B: RT = 13.2min; MS (m+1) = 352.3; ^1H NMR (400MHz, $CDCl_3$) 7.3 (s, 5H), 7.2 (dd, 2H), 6.8 (dd, 2H), 4.0 (br t, 2H), 3.3, (br, 1H), 3.1 (br, 1H), 2.5-1.2 (13H).

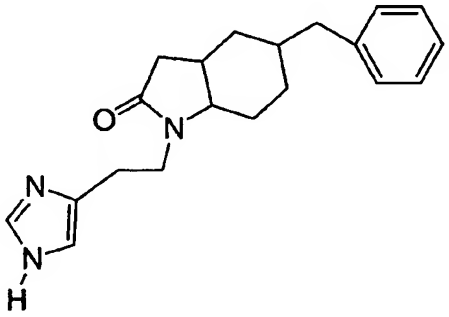
EXAMPLE 5



5-Benzyl-1-[2-(1H-imidazol-4-yl)-ethyl]-octahydro-indole

Example 5 was prepared by the following procedure.

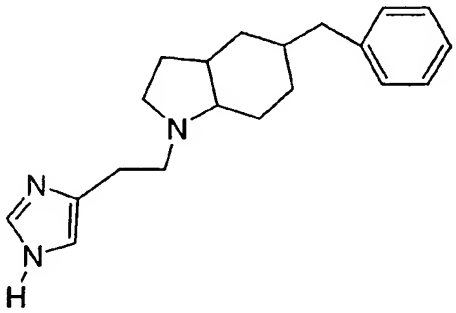
Step 1:



5-Benzyl-1-[2-(1H-imidazol-4-yl)-ethyl]-octahydro-indol-2-one:

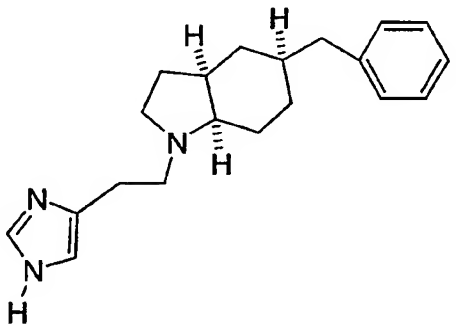
Step 1 followed a procedure similar to that described above for 1,5-dibenzyl-octahydro-indol-2-one in Example 1, Step 6, but substituting histidine for benzylamine. After chromatography eluting with 90:10 $CHCl_3$: MeOH, 5-benzyl-1-[2-(1H-imidazol-4-yl)-ethyl]-octahydro-indol-2-one was obtained as a resin.

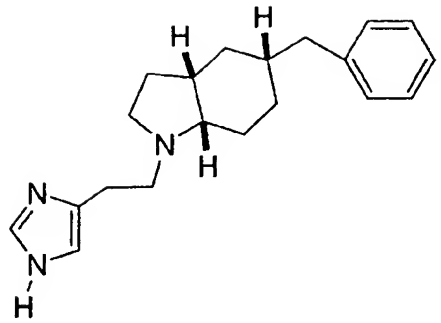
Step 2:



5-Benzyl-1-[2-(1H-imidazol-4-yl)-ethyl]-octahydro-indole:

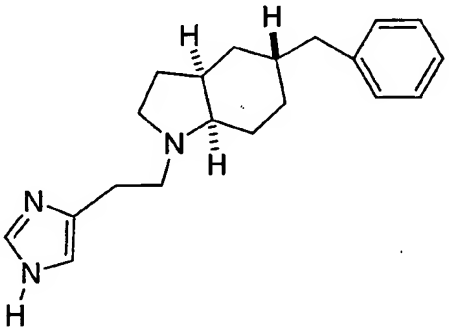
In a manner similar to described for 1,5-dibenzyl-octahydro-indol-2-one above in Example 1, Step 7, but substituting 5-benzyl-1-[2-(1H-imidazol-4-yl)-ethyl]-octahydro-indol-2-one for 1,5-dibenzyl-octahydro-indol-2-one, gave 5-benzyl-1-[2-(1H-imidazol-4-yl)-ethyl]-octahydro-indole.
MS (m+1) = 310.4. Chromatography eluting with 90:10:1 $CHCl_3$:MeOH:NH_4OH gave first (±)-5-cis-benzyl-1-[3-(3H-imidazol-4-yl)-ethyl]-cis-octahydro-indole:

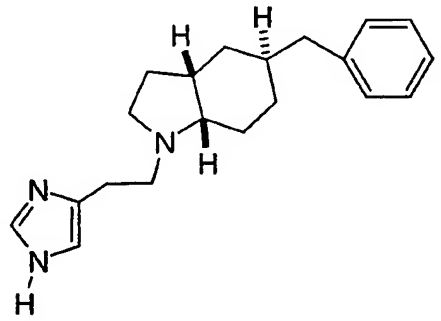




MS (m+1) = 310.4; ^{1}H NMR (400 MHz, $CDCl_3$) 7.4- 7.1 (complex m, 6H), 6.8 (d, 1H), 3.4-0.9 (complex, 19 H).

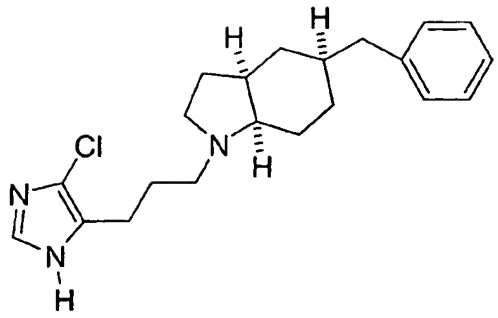
Later fractions contained the minor isomer (±)-5-trans-benzyl-1-[3-(3H-imidazol-4-yl)-ethyl]-cis-octahydro-indole:



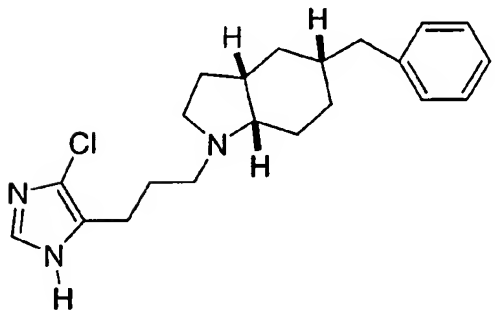


MS (m+1) = 310.4; ^{1}H NMR (400 MHz, $CDCl_3$) 7.6 (s, 0.5H), 7.4 (s, 0.5H), 7.35-7.1 (complex m, 5H), 6.8 (m, 1H), 3.4-0.9 (complex, 19 H).

EXAMPLE 6



(Ex. 6A)

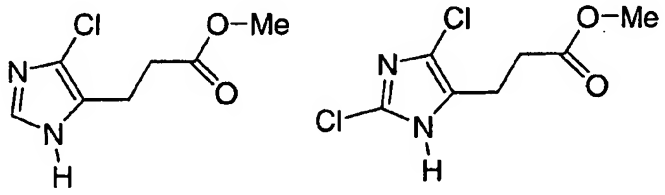


(Ex. 6B)

(±)-5-cis-Benzyl-1[3-(5-chloro-3H-imidazol-4-yl)-propyl]-cis-octahydro-indole

Example 6 was prepared by the following procedure.

Step 1:

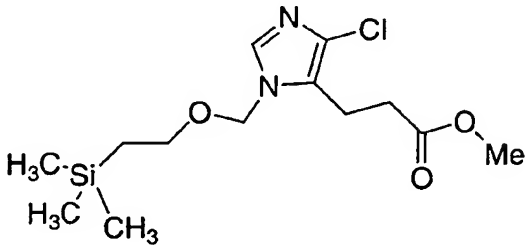


3-(5-Chloro-3H-imidazol-4-yl)-propionic acid methyl ester and 3-(2,5-dichloro-3H-imidazol-4-yl)-propionic acid methyl ester:

Chlorination of 3-(3H-imidazol-4-yl)-propionic acid methyl ester using the procedure described in R. Jain, B. Avramovitch and L.A. Cohen, *Tetrahedron*, 54:3235-3242(1998) with N-chlorosuccinimide in acetonitrile gave after chromatography on silica gel, eluting with ethyl acetate, gave 3-(2,5-dichloro-3H-

imidazol-4-yl)-propionic acid methyl ester as a solid. Later fractions gave 3-(5-chloro-3H-imidazol-4-yl)-propionic acid methyl ester as a solid.

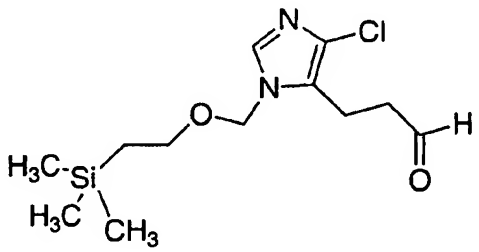
Step 2:



3-[5-Chloro-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-propionic acid methyl ester:

A mixture of 0.40g of 3-(5-chloro-3H-imidazol-4-yl)-propionic acid methyl ester, 0.5mL of N,N-diisopropylethylamine, 15mL of dichloromethane and 0.4mL of 2-(trimethylsilyl)ethoxymethyl chloride was stirred at room temperature for 24h. The reaction mixture was diluted with 50mL chloroform and 10mL saturated aqueous Na_2CO_3 and the layers separated. The aqueous layer was extracted with 2X25mL of chloroform and the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure. Purification by chromatography eluting with ethyl acetate gave 0.8g of 3-[5-chloro-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-propionic acid methyl ester as an oil.

Step 3:

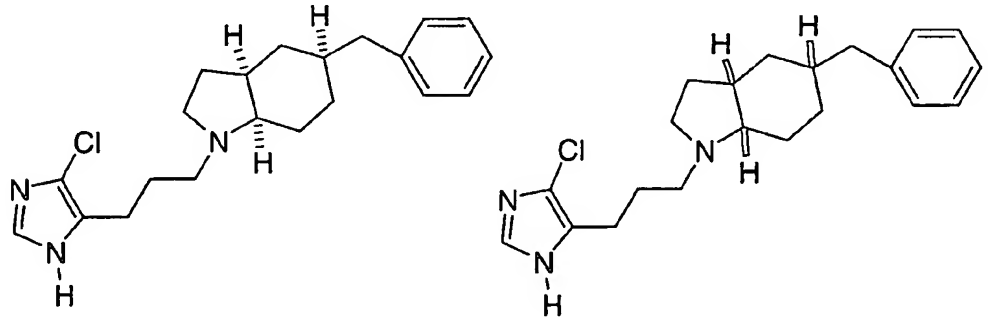


3-[5-Chloro-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-propionaldehyde:

To a solution of 0.20g of 3-[5-chloro-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-propionic acid methyl ester in 10mL of toluene

cooled to –75°C under nitrogen was added 0.5mL of 1.5 M diisobutylaluminum hydride. After 1h at –75°C, the reaction was quenched with 0.2mL of methanol, allowed to warm to room temperature over 30min and partitioned between 1N sodium carbonate and ethyl acetate. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude 3-[5-chloro-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-propionaldehyde (0.2 g) was essentially homogeneous by TLC, eluting with ethyl acetate.

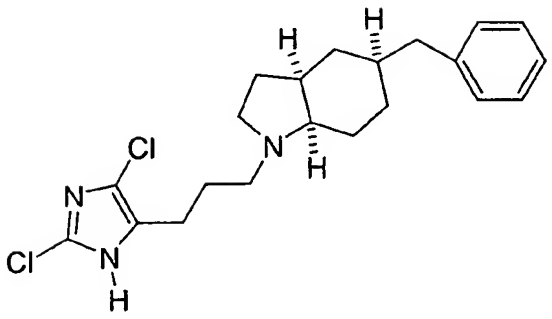
Step 4:



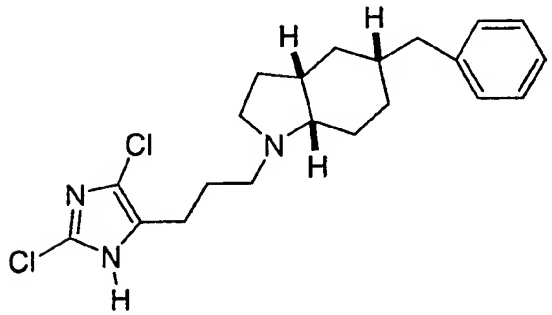
(±)-5-cis-Benzyl-1[3-(5-chloro-3H-imidazol-4-yl)-propyl]-cis-octahydro-indole

A mixture of 0.10g of (±)-cis-5-benzyl-cis-octahydro-indole, 0.2g of 3-[5-chloro-3-(2-trimethylsilanyl-ethoxymethyl)-3H-imidazol-4-yl]-propionaldehyde, 5mL of 1,2-dichloroethane and 0.25g of sodium triacetoxyborohydride was stirred at room temperature for 48h. The reaction mixture was diluted with 50mL chloroform and 10mL saturated aqueous Na_2CO_3 and the layers separated. The aqueous layer was extracted with 2X25mL of chloroform and the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure. The crude SEM-protected 5-benzyl-1-[3-(5-chloro-3H-imidazol-4-yl)-propyl]-octahydro-indole was deprotected by refluxing 2h in 20mL of ethanol and 2mL of 6N HCl. The mixture was concentrated to dryness, partitioned between aqueous sodium carbonate and chloroform, and the combined chloroform extracts dried over magnesium sulfate and concentrated. Purification by chromatography eluting with 90:10:1 $CHCl_3$:MeOH:NH_4OH gave 0.15g (±)-5-cis-benzyl-1[3-(5-chloro-3H-imidazol-4-yl)-propyl]-cis-octahydro-indole: MS (m+1) = 358.2; ^1H NMR (400MHz, $CDCl_3$) 7.3 –7.0 (m, 6H), 3.3 (dd, 1H), 2.95 (m, 2H), 2.55 (m, 3H), 2.4, 2.3, 2.25, 2.0, 1.85, 1.7, 1.7, 1.5, 1.1 (complex, 15 H).

EXAMPLE 7



(Ex. 7A)

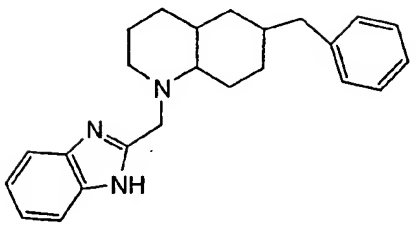


(Ex. 7B)

(±)-5-cis-Benzyl-1[3-(2,5-dichloro-3H-imidazol-4-yl)-propyl]-cis-octahydro-indole

Example 7 was prepared in a manner similar to the procedure described above for (±)-5-cis-benzyl-1[3-(5-chloro-3H-imidazol-4-yl)-propyl]-cis-octahydro-indole, Example 6. Substituting 3-(2,5-dichloro-3H-imidazol-4-yl)-propionic acid methyl ester for 3-(2-chloro-3H-imidazol-4-yl)-propionic acid methyl ester in Step 2, gave (±)-5-cis-benzyl-1[3-(2,5-dichloro-3H-imidazol-4-yl)-propyl]-cis-octahydro-indole: MS (m+2) = 354.2; ^{1}H NMR (400MHz, $CDCl_3$) 10.2 (br s, 1H), 7.3 –7.0 (m, 5H), 3.25 (dd, 1H), 2.95 (m, 1H), 2.9 (m, 1H), 2.55 (m, 3H), 2.45, 2.3, 2.1, 2.0, 1.7-1.35, 1.1 (complex, 15 H).

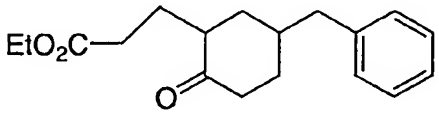
EXAMPLE 8



1-(1H-Benzimidazol-2-ylmethyl)-6-benzyl-decahydro-quinoline

Example 8 was prepared by the following procedure.

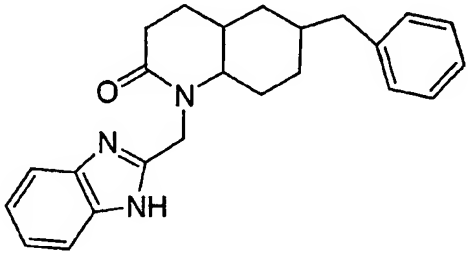
Step 1:



3-(5-Benzyl-2-oxo-cyclohexyl)-propionic acid ethyl ester:

A solution of 1g of the crude 1-(4-benzyl-cyclohex-1-enyl)-pyrrolidine and 1mL of ethyl acrylate in 20mL of dioxane was heated at reflux for 3h, cooled and concentrated under reduced pressure. The resulting residue was diluted with 10mL of water and 10mL of 10% sulfuric acid and extracted into 2X100mL of ether. The combined extracts were dried over magnesium sulfate and concentrated under reduced pressure. Drying under vacuum gave 0.74g of crude 3-(5-benzyl-2-oxo-cyclohexyl)-propionic acid ethyl ester as an oil.

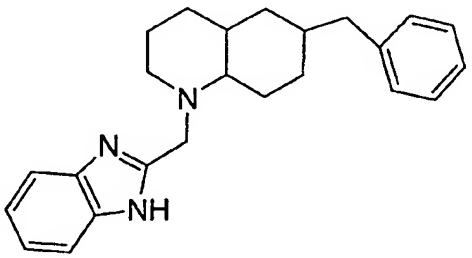
Step 2:



1-(1H-Benzimidazol-2-ylmethyl)-6-benzyl-octahydro-quinolin-2-one:

A mixture of 0.74g of 3-(5-benzyl-2-oxo-cyclohexyl)-propionic acid ethyl ester, 0.572g of 2-aminomethylbenzimidazole dihydrochloride, 10mL of 1,2-dichloroethane, 0.40g of sodium acetate and 0.74g of sodium triacetoxyborohydride was stirred at room temperature for 48h. The reaction mixture was diluted with 100mL chloroform and 40mL saturated aqueous Na_2CO_3 and the layers separated. The aqueous layer was extracted with 2X25mL of chloroform and the combined organic layers dried over magnesium sulfate and concentrated under reduced pressure. Purification by chromatography eluting with a gradient of ethyl acetate to 10% methanol in ethyl acetate gave 0.15g of 1-(1H-benzimidazol-2-ylmethyl)-6-benzyl-octahydro-quinolin-2-one.

Step 3:



1-(1H-Benzimidazol-2-ylmethyl)-6-benzyl-decahydro-quinoline :

A stirred solution of 0.15g of 1-(1H-benzimidazol-2-ylmethyl)-6-benzyl-octahydro-quinolin-2-one in 20mL of dry THF containing 0.1g of lithium aluminum hydride was heated to reflux overnight, cooled in an ice bath, and quenched with 0.1mL of 5N NaOH, then 1mL of water. After stirring and warming to room temperature for 2h, the mixture was filtered through a glass frit and the filtrate concentrated to dryness under reduced pressure. Chromatography using 10% methanol in chloroform gave 1-(1H-benzimidazol-2-ylmethyl)-6-benzyl-decahydro-quinoline in four bands.

Isomer A: MS (m+1) = 360.2; ^1H NMR (400MHz, $CDCl_3$) 9.2 (br, 1H), 7.6 (br, 1H), 7.5 (br, 1H), 7.25 (m, 7H), 4.2 (d, 1H), 3.4 (d, 1H), 2.7 (d, 1H), 2.6 (d, 2H), 2.2 (d, 1H), 2.05 (t, 1H), 1.8-1.1 (complex, 12H).

cis-1-(1H-benzimidazol-2-ylmethyl)-6-cis-benzyl-decahydro-quinoline

Isomer B: MS (m+1) = 360.2; ^1H NMR (400MHz, $CDCl_3$) 9.8 (br, 1H), 7.6 (br, 2H),

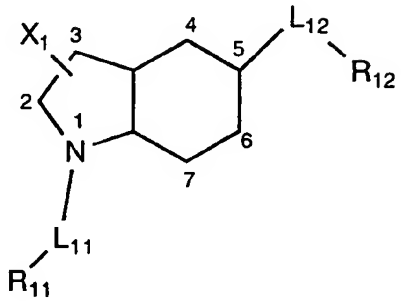
7.25 (m, 7H), 4.3 (m, 1H), 4.0 (dd, 2H), 3.5 (dd, 1H), 2.45 (dd, 2H), 2.8-1.1 (complex, 13H).

Isomer C: MS (m+1) = 360.2; ^{1}H NMR (400MHz, $CDCl_3$) 9.8 (br, 1H), 7.6 (br, 2H), 7.25 (m, 7H), 4.1 (m, 1H), 4.0 (m, 1H), 2.8 (m, 1H), 2.6 (d, 2H), 2.5-1.1 (complex, 14H)

Isomer D: MS (m+1) = 360.2; ^{1}H NMR (400MHz, $CDCl_3$) 9.8 (br, 1H), 7.6 (br, 2H), 7.2 (m, 7H), 4.6 (m, 1H), 4.1 (m, 2H), 2.5 (d, 2H), 4.0-1.0 (complex, 14H).

WHAT IS CLAIMED IS:

1. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

R_{11} is 2-benzimidazole, 4-imidazole, 2-imidazopyridine, 2-indole, 2-quinazoline, or 4-phenol; each optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

R_{12} is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

L_{11} is C_1-C_4alkyl, C_1-C_4alkenyl, C_1-C_4alkynyl, C_1-C_4alkoxy, aminoC_1-C_4alkyl, hydroxyC_1-C_4alkyl, carbonyl, cycloC_3-C_6alkyl or aminocarbonyl;

L_{12} is phenylmethyl or phenylmethylaminocarbonyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, or methyl; and

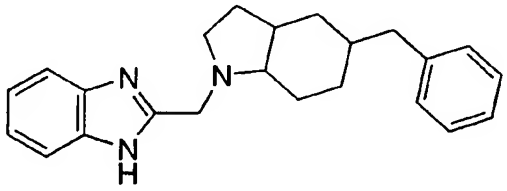
optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X_1, wherein X_1 is hydroxy, amino C_1-C_4alkylamino, di(C_1-C_4)alkylamino, C_1-C_4alkyl, ester, carbamate, carbonate, or ether.

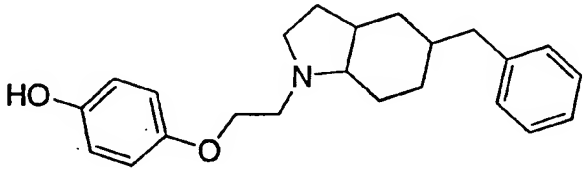
2. The compound according to claim 1, wherein R_{11} is 2-benzimidazole, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy.

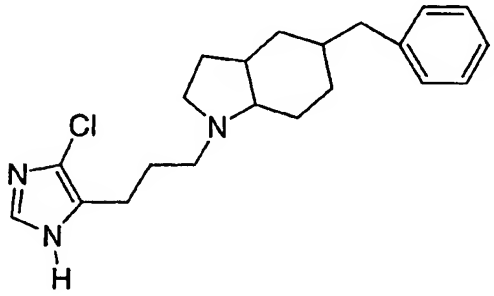
3. The compound according to claim 1, wherein R_{11} is 4-imidazole, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy.

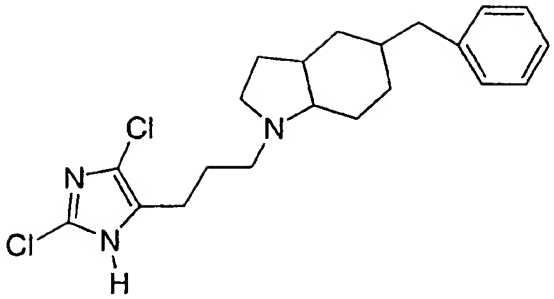
4. The compound according to claim 1, wherein R_{11} is 4-phenol; optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy.

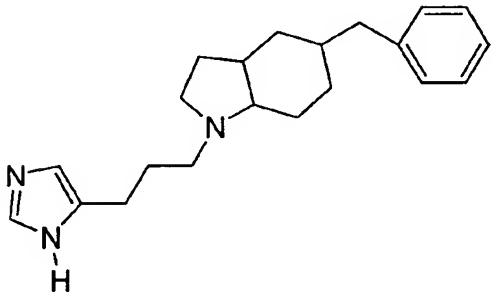
5. The compound according to claim 1, comprising

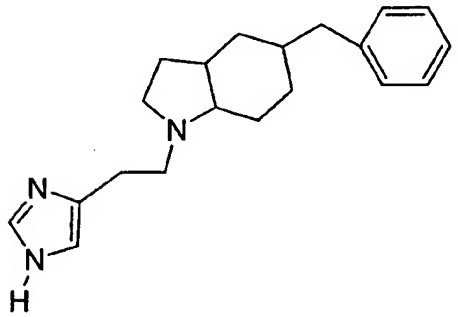












or a pharmaceutically acceptable salt thereof.

6. The compound according to claim 1 comprising:

2-(5-cis-Benzyl-cis-octahydro-indol-1-ylmethyl)-1H-benzimidazole;

2-(5-trans-Benzyl-cis-octahydro-indol-1-ylmethyl)-1H-benzimidazole;

(±)-5-cis-Benzyl-1-[3-(3H-imidazol-4-yl)-propyl]-cis-octahydro-indole;

4-[2-(5-Benzyl-octahydro-indol-1-yl)-ethoxy]-phenol;

5-Benzyl-1-[2-(1H-imidazol-4-yl)-ethyl]-octahydro-indole;

(±)-5-cis-Benzyl-1[3-(5-chloro-3H-imidazol-4-yl)-propyl]-cis-octahydro-indole; or

(±)-5-cis-Benzyl-1[3-(2,5-dichloro-3H-imidazol-4-yl)-propyl]-cis-octahydro-indole.

7. A pharmaceutical composition comprising an inert carrier and an effective amount of a compound according to claim 1.

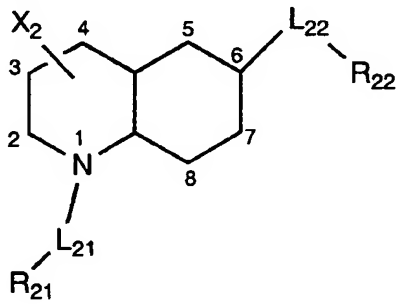
8. The pharmaceutical composition according to claim 7 useful for the treatment of pain.

9. The pharmaceutical composition according to claim 7 useful for the treatment of migraine, depression, anxiety, schizophrenia, Parkinson's disease, or stroke.

10. A method of treating pain comprising a step of administering to one in need of such treatment an effective amount of a compound according to claim 1.

11. A method of treating migraine, depression, anxiety, schizophrenia, Parkinson's disease, or stroke comprising a step of administering to one in need of such treatment an effective amount of a compound according to claim 1.

12. A compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein

R_{21} is 2-benzimidazole, 4-imidazole, 2-imidazopyridine, 2-indole, 2-quinazoline, or 4-phenol; each optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

R_{22} is phenyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy;

L_{21} is C_1-C_4alkyl, C_1-C_4alkenyl, C_1-C_4alkynyl, C_1-C_4alkoxy, aminoC_1-C_4alkyl, hydroxyC_1-C_4alkyl, carbonyl, cycloC_3-C_6alkyl or aminocarbonyl;

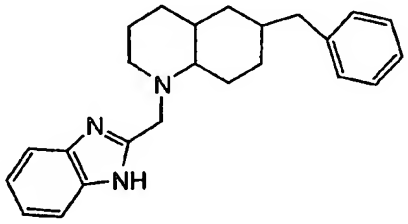
L_{22} is phenylmethyl or phenylmethylaminocarbonyl, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, or methyl; and

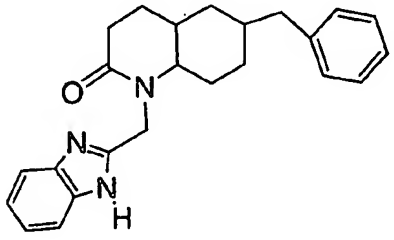
optionally substituted at any of the 2, 3, 4, 6, or 7 positions independently with X2, wherein X_2 is hydroxy, amino C_1-C_4alkylamino, di(C_1-C_4)alkylamino, C_1-C_4alkyl, ester, carbamate, carbonate, or ether.

13. The compound according to claim 12, wherein R_{21} is 2-benzimidazole, optionally substituted with one to five substituents, each substituent independently being chloro, fluoro, bromo, C_1-C_4alkyl, trifluoromethyl, hydroxy, or carboxy.

14. The compound according to claim 12, wherein said compound is 1-(1H-Benzimidazol-2-ylmethyl)-6-benzyl-decahydro-quinoline.

15. The compound according to claim 12, comprising





or a pharmaceutically acceptable salt thereof.

16. A pharmaceutical composition comprising an inert carrier and an effective amount of a compound according to claim 12.

17. The pharmaceutical composition according to claim 16 useful for the treatment of pain.

18. The pharmaceutical composition according to claim 16 useful for the treatment of migraine, depression, anxiety, schizophrenia, Parkinson's disease, or stroke.

19. A method of treating pain comprising a step of administering to one in need of such treatment an effective amount of a compound according to claim 12.

20. A method of treating migraine, depression, anxiety, schizophrenia, Parkinson's disease, or stroke comprising a step of administering to one in need of such treatment an effective amount of a compound according to claim 12.